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Original Article

Design, Synthesis and Characterization of Some Impurities of Rivaroxaban: An Oral Anticoagulant

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ABSTRACT

Background: The quality, safety, and regulatory compliance of rivaroxaban, an oral anticoagulant that is often prescribed. According to International Council for Harmonization (ICH) recommendations, impurity profiling, the development of analytical methods, and quality assurance all depend on well-characterized impurity reference standards. **Objectives:** In order to create reliable impurity reference standard for pharmaceutical quality control and regulatory purposes, the current study aimed to design, synthesize, purify, and characterize specific rivaroxaban-related impurities. **Materials and Methods:** A series of organic processes involving reduction, epoxide formation, dimerization, and epoxide ring-opening reactions were used to create five rivaroxaban-related impurities: Rivaroxaban Impurity APM, N-Glycidyl Phthalimide, Phthalimido Morpholinone (or Phthalimido Descarbonyl, depending on your final nomenclature), Diphthalimido Morpholinone, and Rivaroxaban Impurity G. Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR), and High-Resolution Mass Spectrometry (HRMS/FTICR-MS) were used to characterize the produced compounds after they had been purified using the proper purification procedures **Results:** The synthesis of all five of the specified impurities was accomplished with acceptable yields and purity. The effective synthesis and structural confirmation of the impurity reference standards were demonstrated by the analytical data from FTIR, NMR, and HRMS, which were in agreement with the predicted molecular structures. **Conclusion:** The established synthetic pathways offer effective and repeatable ways to prepare significant impurities associated to rivaroxaban. During the development, production, and quality control of rivaroxaban pharmaceutical formulations, the produced and thoroughly defined impurity reference standards can help with impurity identification, analytical technique validation, and regulatory compliance.

Keywords: Anticoagulant, Impurities, Oxazolidinone, Reference Standard, Rivaroxaban.

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INTRODUCTION

The purity of a pharmaceutical product is assessed by determining the proportion of the Active Pharmaceutical Ingredient (API) present using validated analytical techniques.[1,2] A drug substance may still be regarded as impure if it contains unintended contaminants, even when these impurities exhibit therapeutic activity comparable to or greater than that of the API. This is because impurities possessing enhanced pharmacological activity or undesirable toxicological properties can compromise the safety, quality and regulatory acceptability of the final product.[3,4] Regulatory agencies such as International Council for Harmonisation (ICH), United States Food and Drug Administration (USFDA), Health Canada and others are increasingly focusing on identifying impurities in API' s and ensuring that purity standards are met.

A key aspect of impurity profiling is the synthesis of compounds possessing the proposed structure. The structural features of an impurity are directly reflected in its spectroscopic characteristics. Functional groups, molecular framework, and stereochemistry influence the spectral pattern obtained by analytical techniques such as Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR), and Mass Spectrometry (MS).[5,6] Comparison of the spectra of synthesized impurity reference standards with those of unknown impurities enables confirmation of molecular structure, identification of functional groups, determination of molecular weight, and differentiation of closely related

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compounds. A systematic strategy for separating and identifying process-related contaminants and degradation products in pharmaceutical substances employing methods like MS, NMR, Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR-MS) has been validated in a number of recent studies.

Rivaroxaban (shown in Figure 1) contains key structural features including an oxazolidinone ring, chlorothiophene ring, morpholinone moiety, and carboxamide linkage, which are essential for its biological activity.[7,8] The oxazolidinone ring is an important structural feature of Rivaroxaban. Under acidic or basic hydrolytic conditions, this ring can undergo cleavage, resulting in ring-opened degradation products. Formation of ring-opening impurities may occur through hydrolysis in acidic or alkaline conditions, elevated temperature and moisture exposure. The ring-opening process typically converts the cyclic oxazolidinone moiety into an open-chain hydroxy-amide derivative.[9,10] These impurities are important because they indicate the degradation pathway of the drug and can affect product stability.

One of the important process-related impurities associated with Rivaroxaban synthesis is as 4-(4-Aminophenyl) Morpholin-3-one (APM) impurity. APM is a key process-related intermediate formed during the synthesis of rivaroxaban. Owing to the presence of its aromatic amino functionality, the compound readily acts as a nucleophile. This compound is a pivotal intermediate in the preparation of the target molecule and contains both an aromatic amino group and a morpholinone ring.

N-Glycidyl Phthalamide impurity is an important chiral synthetic intermediate used in the preparation of Rivaroxaban and its related impurities. The molecule consists of a highly reactive epoxide (oxirane) ring attached to a phthalimide moiety, making it a valuable building block in pharmaceutical synthesis.

Phthalimido Descarbonyl impurity, is formed through the nucleophilic ring-opening reaction between APM impurity and the epoxide intermediate. The amino group attacks the epoxide ring, resulting in the formation of a beta - hydroxy amine derivative containing both morpholinone and phthalimide functionalities.

Diphthalimido Morpholinone impurity is formed by dimerization reaction between N-glycidyl Phthalimide and APM impurity reaction. the amino group attacks the epoxide ring, resulting in the formation of a beta-hydroxy amine derivative containing both morpholinone and phthalimide functionalities.

Rivaroxaban impurity G is formed during cyclization process by using DMAP and CDI. CDI and DMAP were used to facilitate the cyclization of the phthalimido descarbonyl intermediate to form rivaroxaban impurity G. CDI acts as a carbonyl-transfer/cyclization reagent, while DMAP serves as a nucleophilic catalyst that facilitates the reaction. These overall pathways are illustrated in Figure 2.

In this research work, we focus on the design, synthesis, and characterization of five key process-related impurities of Rivaroxaban. Our objective is to produce derivatives of API contaminants and then identify them by characterizing them using different analytical techniques.

MATERIALS AND METHODS

Chemicals and solvents

Methanol, Ethyl acetate, Hexane, Dichloromethane (DCM), Acetonitrile, Ethanol were purchased from Advent Chembio Pvt. Ltd., Mumbai. Potassium carbonate, 4-Dimethylaminopyridine (DMAP), Carbonyldiimidazole (CDI), Phthalamide, Tri phosgene, Epichlorohydrin, 4-(4-Nitrophenyl) morpholin-3-one were purchased from BLD Pharma Tech Pvt. Ltd., Hyderabad. Palladium on Carbon (Pd/C), Tetrahydrofuran (THF), acetone was purchased from Spectrochem Pvt. Ltd., Hyderabad. All chemicals and solvents were of analytical grade and used without further purification unless otherwise stated.

Synthesis of Rivaroxaban Impurity APM

In a Clean Round Bottom Flask (RBF), combine 1 g (4.81 mmol) of 4-(4-Nitrophenyl) morpholin-3-one with 0.10 g (0.094 mmol) of Pd/C at Room Temperature (RT). Add 5 mL of Dimethylformamide (DMF) and 20 mL of Methanol to the mixture and stir for 5 to 10 min. Next, transfer the RBF to an oil bath and adjust the temperature to 100°C. All to the reaction mixture reflux for 12 hr. The H_2 is supplied via balloon at 100 psi. Monitor the progress by Thin Layer Chromatography (TLC) using a mobile phase of DCM and methanol in a 4.5:0.5 ratio. Once the reaction was complete, filter the reaction mixture through a celite bed to remove the pd/C catalyst. Wash the catalyst cake with 15 mL methanol. Combine the filtrate, check the TLC, then concentrate under reduced pressure to yield the target compound. The synthetic scheme is shown in Figure 3.

Synthesis of Rivaroxaban Impurity N-Glycidyl Phthalimide

In a clean RBF, dissolve 1 g (6.75 mmol) of Phthalimide in 0.53 mL (6.75 mmol) of Epichlorohydrin while stirring at 90 C, then add 1.8 g (13.03 mmol) of Potassium Carbonate. The reaction mixture was maintained under constant stirring for 15 min with continuous addition of DMF. Allow it to stir for 10 min. Seal the flask with a stopper and allow the reaction to proceed at 90°C for 12 hr. Reaction advancement was assessed by TLC with a developing solvent mixture of ethyl acetate and Hexane in a 3:7 ratio. Following completion of the reaction, the mixture was quenched with cold water and subsequently worked up using ethyl acetate. Separate the organic and aqueous layers, to extract the crude product. The synthetic scheme shown in Figure 4.

Synthesis of Rivaroxaban Impurity Phthalimido Descarbonyl

In an RBF, dissolve 1 g (5.20 mmol) of APM impurity and 1.05 g (5.17 mmol) of N-Glycidyl phthalimide. Stir for 30 min. Add 18 mL ethanol and 2 mL of water dropwise and continue stirring for 10 min. Seal and keep at 80°C for 15 hr. Monitor by TLC (DCM: Methanol=95:5). The reaction mixture was extracted using ethyl acetate and water. The organic phase was separated and concentrated under reduced pressure to afford the crude product. The synthetic scheme is shown in Figure 5.

Synthesis of Rivaroxaban Impurity Diphthalimido Morpholinone

In an RBF, dissolve 1 g (5.20 mmol) of APM and 2.11 g (10.39 mmol) of N-Glycidyl phthalimide. Stir for 30 min. Add 27 mL ethanol and 3 mL of water dropwise and continue stirring for 10 min. Seal and keep at 80°C for 15 hr. Monitor by TLC (DCM: Methanol=4:1). After completion, partition the reaction mixture between ethyl acetate and water, separate the organic phase, and remove the solvent under vacuum to obtain the crude material. The synthetic scheme is shown in Figure 6.

Synthesis of Rivaroxaban Impurity G

In a clean RBF, dissolve 1 g (2.53 mmol) of Phthalimido Descarbonyl impurity and add 0.410 g (2.52 mmol) of CDI and 100 mg (0.82 mmol) of DMAP. Keep the reaction mixture under stirring for 15 min, then slowly add 20 mL of THF dropwise. Continue stirring for a further 5 to 10 min. The reaction vessel was stoppered and maintain at RT for 24 hr to complete the reaction. The progress of the reaction was evaluated by TLC using a mobile phase of DCM: Methanol in a 4: 1 ratio. Once the reaction reached completion, the mixture was treated with ethyl acetate and water. The organic layer was separated, concentrated under reduced pressure, and the crude product was obtained. The synthetic scheme shown in Figure 7.

Purification of Synthesized Compounds by Column Chromatography

A basic method that is frequently employed for the separation and purification of chemical substances is column chromatography. The method entails moving a liquid mobile phase through a solid stationary phase-filled column; silica gel (Silica gel grade: 240 mm) is used as stationary phase. Polar compounds generally require more polar mobile-phase solvents.[11] (e.g. ethyl acetate, methanol) to elute from a polar stationary phase such as silica gel, whereas nonpolar compounds are eluted using nonpolar solvents such as hexane. Compounds segregate from one another as the mixture moves down the column due to interactions with the stationary adsorbent and carrier solvents because of different affinities.[12,13] Column chromatography is widely used in both scientific and industry contexts and is essential to the isolation and purification of substances.[14] All synthesized impurities were purified using column chromatography with appropriate solvent systems.

METHOD OF ANALYSIS

Thin Layer Chromatography

An aluminium sheet pre- coated with silica gel was used for TLC examination. Under UV light, the spots on the TLC plates were visible.

Infrared Spectroscopy

Using KBr pellets as the sample medium, the infrared spectra of the generated compounds were recorded using a JASCO FTIR-4100 spectrophotometer. The spectra were expressed in wavenumbers (cm^{-1}).

Mass Spectrometry

An Agilent 6320 ion mass spectrometer was used to obtain the mass spectra. When necessary, samples were analysed in either positive or negative ion mode.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were acquired with a MERCURY VARIAN 500 MHz or 400 MHz instrument, using CDCl3 or DMSO-d6 as solvents and TMS as the internal standard. Chemical shifts are reported in delta (ppm).

RESULTS AND DISCUSSION

Five rivaroxaban-related impurities, namely Rivaroxaban Impurity APM, N-Glycidyl Phthalimide, Phthalimido Descarbonyl impurity, Diphthalimido Morpholinone impurity, and Rivaroxaban Impurity G, were successfully synthesized using the proposed synthetic routes involving reduction, epoxide formation, dimerization, and epoxide ring-opening reactions. The

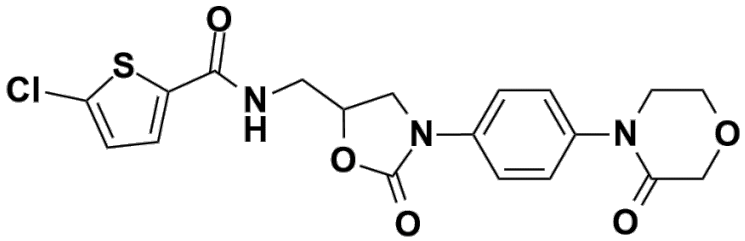


Figure 1: Rivaroxaban Structure.

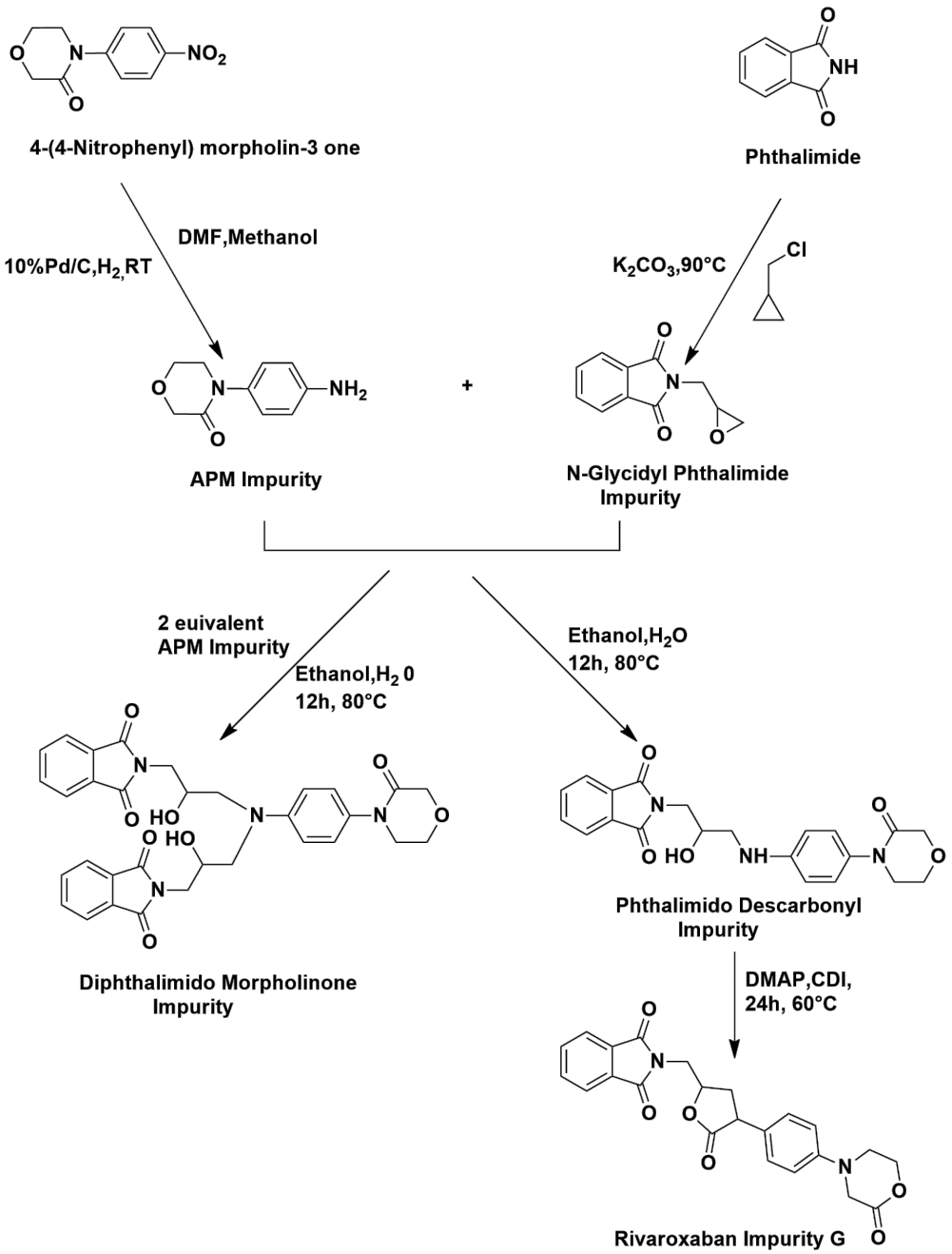


Figure 2: Synthetic Scheme for Rivaroxaban and It's Impurities.

synthesized compounds were purified by column chromatography and characterized by ^{1}H NMR and mass spectrometry, confirming their proposed structures. The experimental spectral data were consistent with the expected molecular structures, demonstrating the successful synthesis of all five impurities with satisfactory yields (The physicochemical properties of synthesized impurities are summarized in Table 1). These well-characterized impurities can serve as valuable reference standards for impurity profiling and quality control of rivaroxaban formulations.

Characterization of Rivaroxaban Impurity APM

Physical Properties: MF: C10H12N2O2, MW :192.21 g mol^{-1}, Appearance: Off-white to pale yellow solid, Yield: 79.40%, TLC: DCM: Methanol (4.5:0.5), Retention factor value: 0.15, Solubility: DMSO, DMF, Color: Off white to pale yellow solid, Odor: Slightly amine like smell, pH: Basic (7.5).

In the IR spectrum (KBr cm $^{-1)}$, this compound containing N-H stretching at 3360-3380 cm^{-1}, C=O stretching at 1660-1680 cm^{-1}, C-O stretching at 1200-1250 cm^{-1} and aromatic C-H stretching at 3000-3100 cm^{-1}.

^{1}H NMR (400 MHz, DMSO -D6) delta ppm: 6.96-6.94 (d, 2H, Ar-H) and 6.56-6.53 (d, 2H, Ar-H) corresponding to the 4 (Ar-H) of the para-substituted phenyl rings. 5.11 (s, 1H, NH2) assigned to the hydroxyl proton. 4.13-3.89 (m, 2H, CH2-O) corresponding to methylene protons adjacent to oxygen. 3.75-3.56 (m, 3H, CH and CH2-N) assigned. 3.35 (m, 1H, CH). 2.50 ppm (s) corresponds to residual DMSO-d6 solvent.

The mass spectrometry data for C10H12N2O2 indicate a calculated M.W of 192.21 g mol-1, with experimental mass-to-charge ratios of 193.2 (M+H) and 215.2 (M+Na).

Characterization of Rivaroxaban Impurity N-Glycidyl Phthalamide

Physical Properties: MF: $C_{11}H_9NO_3$, MW: 203.20 g mol^{-1}, Appearance: White crystalline solid, Yield: 65.20%, TLC: Ethyl acetate: Hexane (3: 7), Rf value: 0.42, Solubility: DMSO, DMF, Ethyl acetate, Color: White crystalline solid, Odor: Odourless.

In the IR spectrum (KBr, cm^{-1}), this compound contains C=O stretching (phthalimide) at 1770-1710 cm^{-1}, C-O-C stretching (epoxide) at 1250-1220 cm$^{-1,}$ aromatic C-H stretching at 3060-3010 cm^{-1}, epoxide ring breathing at 860-830 cm^{-1} and N-CH_2 stretching at 2950-2850 cm^{-1}.

1H NMR (400 MHz, CDCL3) delta ppm: 7.73-7.88 (m, 4H) corresponding to the aromatic protons of the phthalimide ring. 3.94-3.99 (m, 1H) assigned to the epoxide methine proton (CH of glycidyl group). 3.78-3.87 (m, 2H) corresponding to the N-CH_2 protons attached to the phthalimide nitrogen. 3.23-3.26 (m, 1H) and 2.70-2.82 (m, 2H) assigned to the epoxide ring methylene protons (CH_2 of oxirane ring).

The mass spectrometry data for C11H9NO3 indicate a calculated MW of 203.20 gmol^{-1}, with experimental mass-to- charge ratios of 204.2 (M+H) and 226.2 (M+Na).

Characterization of Rivaroxaban Impurity Phthalimido Descarbonyl

Physical Properties

MF: $C_{21}H_{21}N_3O5$, MW: 395.5 g mol^{-1}, Appearance: Pale yellow solid, Yield: 62.30%, TLC: DCM: Methanol (95:5), R_f value: 0.38, Solubility: DMSO, DMF, Methanol, Color: Pale yellow solid, Odor: Slightly amine like smell, pH: Basic (7.2).

In the IR spectrum (KBr, cm^{-1}), this compound features O-H stretching at 3450-3350 cm^{-1} (broad), N-H stretching (secondary amine) at 3320-3280 cm^{-1} C=O stretching (phthalimide) at 1770-1710 cm^{-1}, C=O stretching (morpholinone) at 1660-1680 cm$^{-1,}$ C-O stretching at 1200-1250 cm^{-1} and aromatic C-H stretching at 3000-3100 cm^{-1}.

^{1}H NMR (400 MHz DMSO-d6) delta ppm: 7.82-7.88 (m, 4H) corresponding to the aromatic protons of the phthalimide ring (4H). 7.03 (d, 2H, J approximately 8 Hz) corresponding to the aromatic protons of the substituted phenyl ring (2H). 6.62 (d,2H, J approximately 8 Hz) corresponding to the aromatic protons of the substitute phenyl ring (2H).5.17(m,4H) corresponding to the aromatic protons of the substituted phenyl ring (2H) 5.17(m,1H) assigned to the hydroxyl-bearing methine proton (CHOH,1H) 4.00-4.13 (m,4H) corresponding to the morpholinone and side -chain methylene and side-chain methylene protons adjacent to oxygen (4H).

3.58-3.92 (m, 6H) assigned to the N-CH_2 and O-CH_2 protons of the morpholinone and hydroxypropyl chain (6H). 3.00-3.25 (m, 2H) corresponding to the methylene protons adjacent to nitrogen (2H).

The mass spectroscopy data for C21H21N3O5 indicate a calculated MW of 395.5 g mol^{-1}, with experimental mass- to-charge ratios of 396.5 (M+H) and 418.5 (M+Na).

Characterization of Rivaroxaban Impurity Diphthalimido Morpholinone

Physical Properties

MF: C32H30N4O8, MW:598.6 g mol^{-1}, Appearance: Yellow solid, Yield: 52.60%, TLC: DCM: Methanol (4:1), R_f value: 0.25, Solubility: DMSO, DMF, Color: Yellow solid, Odor: Odourless, pH: Neutral (6.8).

In the IR spectrum (KBr, cm-$^{1)}$, this compound contains O-H stretching (hydroxyl) at 3371 cm^{-1} (broad), C=O stretching (phthalimide, 4 carbonyls) at 1776-1710 cm^{-1}, C=O stretching (morpholinone) at 1660-1630 cm^{-1}, C-O Stretching at 1200-1000

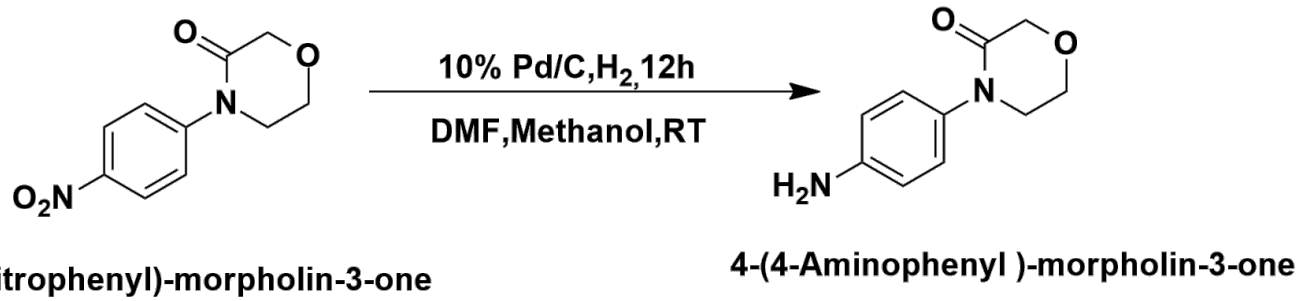


Figure 3: Synthesis of 4-(4-Aminophenyl) morpholin-3-one (Impurity APM).

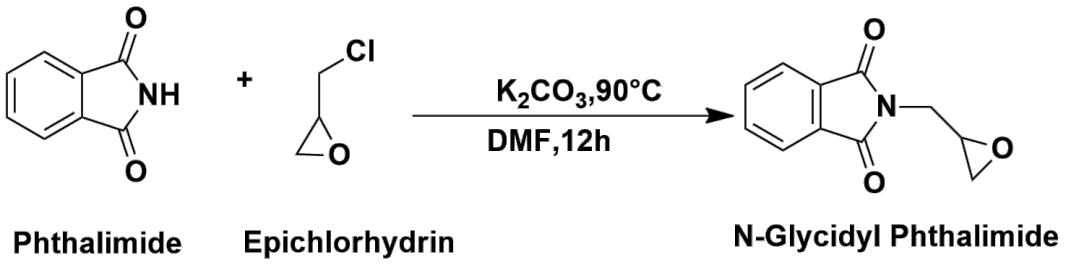


Figure 4: Synthesis of N-Glycidyl Phthalimide.

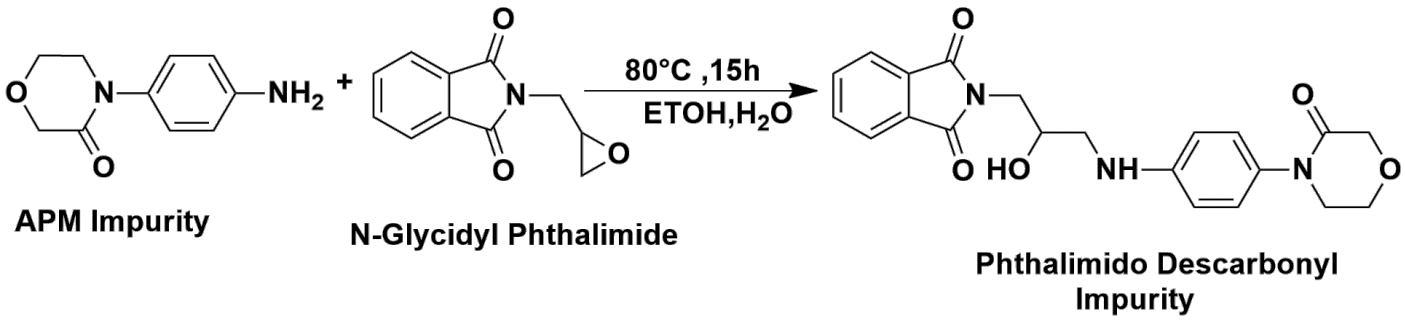


Figure 5: Synthesis of Phthalimido Descarbonyl Impurity.

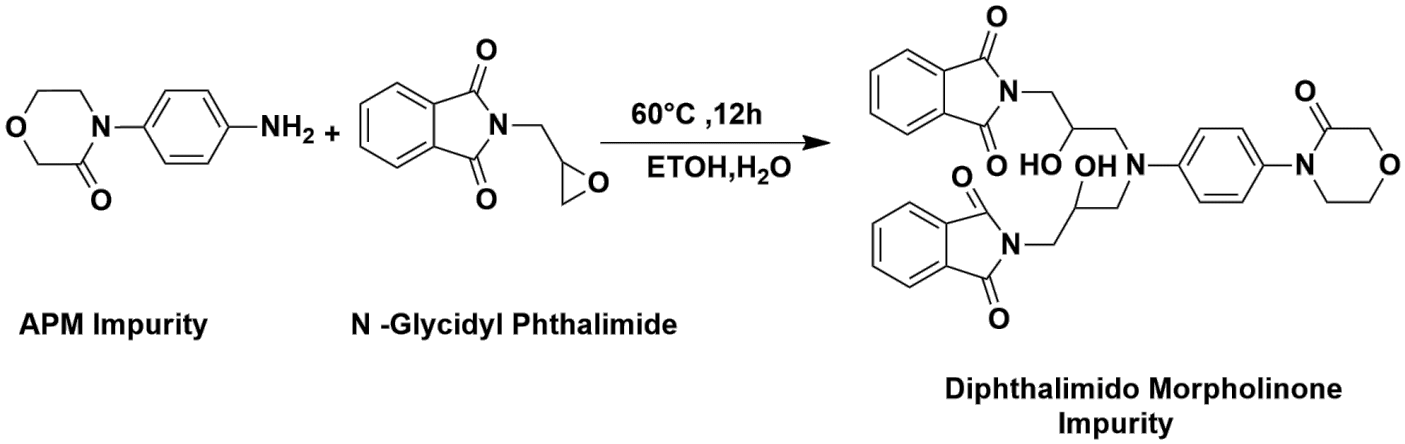


Figure 6: Synthesis of Diphthalimido Morpholinone Impurity.

cm^{-1}, aromatic C-H stretching at 3000-2900 cm^{-1} and N-CH_2 stretching at 2900-2850 cm^{-1}, C=C Stretching at 1633 cm^{-1}.

^{1}HNMR (400 MHz, DMSO-d6) delta ppm: 7.82-7.88 (m,8H) corresponding to the aromatic protons of the two phthalimide rings (8H). 6.60-7.05 (d, 4H, J approximately 8 Hz) corresponding to the aromatic protons of the para-substituted phenyl ring (4H). 5.15-5.65 (m, 2H) assigned to the methine protons attached to hydroxyl-bearing carbons (CHOH, 2H). 3.90-4.20 (m, 8H) corresponding to the O-CH_2 and morpholinone methylene protons (8H). 3.10-80 (m, 10H) assigned to the N-CH_2 and remaining aliphatic methylene protons of the dimeric side chains (10H).

The mass spectrometry data for C32H30N4O8 indicate a calculated M.W of 598.6 g mol^{-1} indicate a calculated. M.W of 598.6 g mol^{-1}, with experimental mass-to- charge ratios of 599.6 (M+H) and 621.59 (M+Na).

Characterization of Rivaroxaban Impurity G

Physical Properties

MF: C22H19N3O6, MW: 421.41 g mol^{-1}, Appearance: White solid, Yield: 45.80%, TLC: DCM: Methanol (4:1), R_f value: 0.32, Solubility: DMSO, DMF, Ethyl acetate, Color: White solid, Odor: Odourless, pH: Neutral (7.0).

The mass spectrometry data for C22H19N3O6 indicate a calculated M.W of 421.41 g mol^{-1}, with experimental mass-to-charge ratios of 422.41 (M+H) and 444.41 (M+Na).

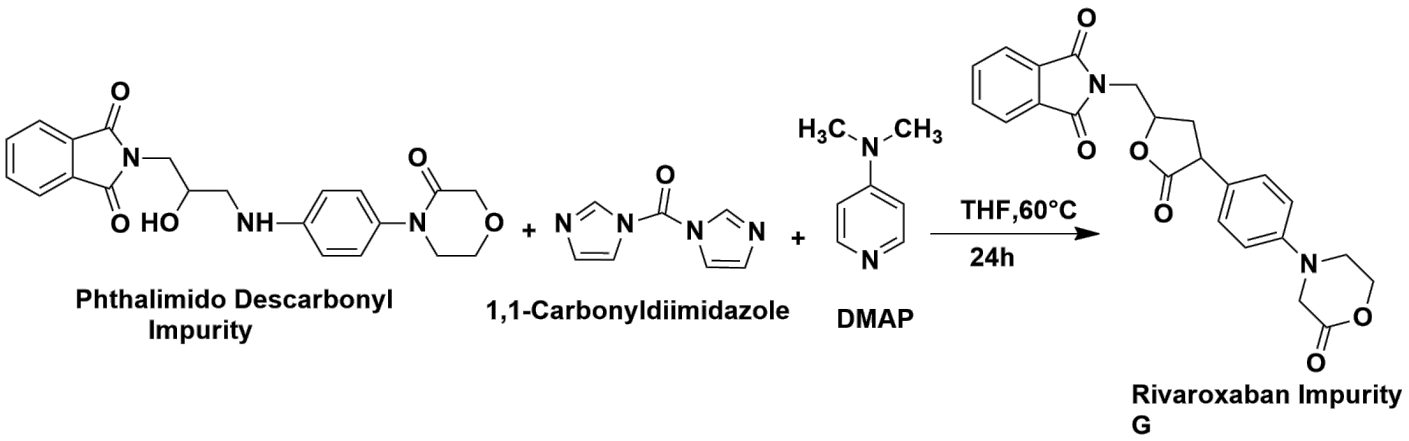
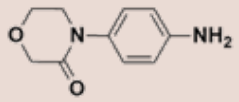
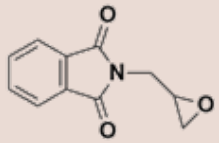
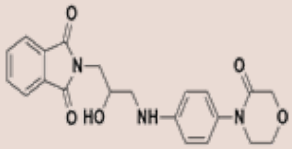
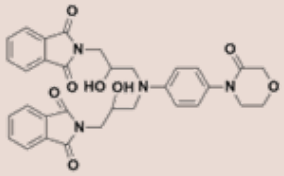
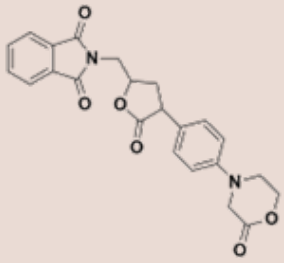


Figure 7: Synthesis of Rivaroxaban G Impurity.

Table 1: Properties of Synthesized Impurities.

Sl. No.	Impurity Structure	Name of Impurity	Molecular Formula and Weight	Melting point	Appearance	Yield (%)
1.		Rivaroxaban Impurity APM:4-(4- Amino phenyl) morpholin-3-one	C10H12N2O2 192.21 g/mol	171-175°C	Off-white solid	79.40%
2.		N-Glycidyl Phthalimide: 2-(Oxirane -2-yl methyl) isoindoline -1,3 dione	C11H9NO3 203.20 g/mol	100-104°C	White solid	65.20%
3.		Phthalimido Descarbonyl: 2-(2-Hydro-3((4-(3-oxomorpholinyl) phenyl) amino) propyl) isoindoline-1,3-dione	C21H21N3O5 395.41 g/mol	208-211°C	Pale yellow solid	62.30%
4.		Diphthalimido Morpholinone: 2,2'-((4-(3-oxomorpholino) phenyl) azanediyl) bis (isoindoline-1,3dione	C32H30N4O8 598.6g/mol	182-184°C	Yellow solid	52.60%
5.		Rivaroxaban Impurity G: 2-((5)-2-oxomorpholin -4-yl) phenyl)-1,3 -oxazolidin -5 ylmethyl) isoindoline-1,3(2H)-di one	C22H19N3O6 421.4 g/mol	213-215°C	White solid	45.80%

CONCLUSION

The synthesis of Rivaroxaban Impurity APM was achieved through catalytic hydrogenation of 4-(4-Nitrophenyl) morpholin-3-one using Pd/C catalyst at 100°C in DMF/Methanol solvent system, yielding 79.40% of the product. This is a key intermediate in Rivaroxaban synthesis and an important process-related impurity.

The synthesis of N-Glycidyl Phthalimide was accomplished by reacting Phthalimide with epichlorohydrin. The mixture was heated at 90°C for 12 hr in DMF with potassium carbonate serving as the base with a yield of 65.20%. This epoxide intermediate is crucial for subsequent ring-opening reactions.

The Phthalimido Descarbonyl impurity was synthesized by the nucleophilic ring-opening reaction of N-Glycidyl Phthalimide with APM impurity in ethanol/water at 80°C for 15 hr, yielding 62.30%. This represents an important ring-opened process impurity.

The Diphthalimido Morpholinone impurity was prepared by reacting APM impurity with two equivalents of N-Glycidyl Phthalimide, resulting in a dimeric product with a yield of 52.60 %.

Finally, Rivaroxaban Impurity G was synthesized by cyclization of the Phthalimide Descarbonyl intermediate using CDI and DMAP in THF at room temperature for 24 hr, yielding 45.80%. This impurity contains the characteristic oxazolidinone ring.

These techniques are straightforward, reliable, and will make it easier to synthesize these impurities in labs with high yield.

The synthesized impurities are process-related impurities that should be identified, characterized, and controlled in accordance with ICH Q3A(R^2) and ICH Q3B(R^2). IR, NMR, and MS were used to characterize the appropriate column chromatography used to purify all impurities. The structures of every synthetic molecule were validated by the spectral data but we didn't perform profiling of impurities by any analytical method.

ACKNOWLEDGEMENT

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ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **RBF:** Round-Bottom Flask; **DMF:** Dimethylformamide; **ICH:** International Council for Harmonisation; **USFDA:** United States Food and Drug Administration; **RT:** Room Temperature; **TLC:** Thin-Layer Chromatography; **CDI:** 1,1′-Carbonyldiimidazole; **DMAP:** 4-Dimethylaminopyridine; **THF:** Tetrahydrofuran; **NMR:** Nuclear Magnetic Resonance; **IR:** Infrared; **FTICR:** Fourier Transform Ion Cyclotron Resonance; **FTICR-MS:** Fourier Transform Ion Cyclotron Resonance Mass Spectrometry; **Pd/C:** Palladium on Carbon; **APM:** 4-(4-Aminophenyl)morpholin-3-one; **hr:** Hours; **MF:** Molecular Formula; **min:** Minute; **TMS:** Tetramethylsilane; **MW:** Molecular Weight.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study does not use human or animal subjects for any trials therefore ethics approval and consent to participate are not required.

STATISTICAL ANALYSIS

This study involved only chemical synthesis and analytical Characterization. This study not involved any statistical analysis hence no any statistical tool was used for the given study.

AUTHORS CONTRIBUTION

Conceptualization: Dr. A. S. Tapkir, Dr. A. B. Pathak, S.M. Bhagat. **Methodology, Design:** Dr. A. S. Tapkir, Dr. A. B. Pathak. **Synthesis:** S.S. Salunkhe, S.M. Bhagat. **Characterization:** Dr. A. S. Tapkir, Dr. A. B. Pathak, S.S. Salunkhe, Writing-Original Draft: S.S. Salunkhe, **Formal Analysis:** Dr. A. S. Tapkir, S. N. Rashinkar, Dr. P. D. Choudhari, **Data Curation:** Dr. A. S. Tapkir, **Investigation:** Dr. A. S. Tapkir, **Writing:** S. S. Salunkhe, **Review and Editing:** Dr. A. S. Tapkir, Dr. P. D. Choudhari.

DATA AVAILABILITY AND CONSENT

The datasets generated during the current study are available from the corresponding authors request and also the data has submitted to journal as supplementary file.

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